



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 876 and 892

[Docket No. FDA-2013-N-0195]

Effective Date of Requirement for Premarket Approval for Transilluminator for Breast Evaluation and Sorbent Hemoperfusion System (SHS) Devices for the Treatment of Hepatic Coma and Metabolic Disturbances; Reclassification of SHS Devices for the Treatment of Poisoning and Drug Overdose

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to require the filing of a premarket approval application (PMA) for the transilluminator for breast evaluation and sorbent hemoperfusion system (SHS) devices for the treatment of hepatic coma and metabolic disturbances and to reclassify SHS devices for the treatment of poisoning and drug overdose, a preamendments class III device, into class II (special controls).

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical Devices Act of 1990 (Pub. L. 101-629), the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), among other amendments, established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or

FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification (510(k)) procedures to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a PMA until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval or until the device is subsequently reclassified into class I or class II. Section 515(b)(1) of the FD&C Act directs FDA to issue an order requiring premarket approval for a preamendments class III device.

Although, under the FD&C Act, the manufacturer of class III preamendments device may respond to the call for PMAs by filing a PMA or a notice of completion of a product development protocol (PDP), in practice, the option of filing a notice of completion of a PDP has not been used. For simplicity, although corresponding requirements for PDPs remain available to manufacturers in response to a final order under section 515(b) of the FD&C Act, this document will refer only to the requirement for the filing and receiving approval of a PMA.

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA (126 Stat. 1056) amended section 513(e) of the FD&C Act, changing the mechanism for reclassifying a device from rulemaking to an administrative order. Section 608(b) of FDASIA amended section 515(b) of the FD&C Act changing the mechanism for requiring premarket approval for a

preamendments class III device from rulemaking to an administrative order. Prior to the enactment of FDASIA, FDA published proposed rules under section 515(b) to require PMAs for the transilluminator for breast evaluation and sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances (75 FR 52294 at 52299, August 25, 2010; 77 FR 9610 at 9617, February 17, 2012). FDA also published a proposed rule to reclassify sorbent hemoperfusion for the treatment of poisoning or drug overdose under section 513(e) of the FD&C Act prior to FDASIA (77 FR 9610 at 9617).

Subsequent to the proposed rules, FDA issued a proposed administrative order to comply with the new procedural requirements created by FDASIA when requiring premarket approval for preamendments class III devices or reclassifying preamendments class III devices (78 FR 20268 at 20276, April 4, 2013). Comments submitted to the aforementioned proposed rules and proposed administrative order were considered when developing this final order.

A. Requirement for Premarket Approval Application

FDA is requiring PMAs for the transilluminator for breast evaluation and SHS devices when indicated for the treatment of hepatic coma and metabolic disturbances.

Section 515(b)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order requiring premarket approval for a preamendments class III device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments from all affected stakeholders, including patients, payers, and providers. FDA published a proposed order to require PMAs for the transilluminator for breast evaluation and sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances in the Federal Register of April 4, 2013 (78 FR 20268

at 20276), and has convened classification panels for the transilluminator for breast evaluation and SHS devices when indicated for the treatment of hepatic coma and metabolic disturbances as discussed in this document.

Section 515(b)(3) of the FD&C Act provides that FDA shall, after the close of the comment period on the proposed order, consideration of any comments received, and a meeting of a device classification panel described in section 513(b) of the FD&C Act, issue a final order to require premarket approval or publish a document terminating the proceeding together with the reasons for such termination.

A preamendments class III device may be commercially distributed without a PMA until 90 days after FDA issues a final order (a final rule issued under section 515(b) of the FD&C Act prior to the enactment of FDASIA is considered to be a final order for purposes of section 501(f) of the FD&C Act (21 U.S.C. 351(f))) requiring premarket approval for the device, or 30 months after final classification of the device under section 513 of the FD&C Act, whichever is later. For transilluminator for breast evaluation and sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances, the preamendments class III devices that are the subject of this proposal, the later of these two time periods is the 90-day period. Since these devices were classified in 1995 and 1983, respectively, the 30-month period has expired (60 FR 36639, July 18, 1995, and 48 FR 53012 at 53028, November 23, 1983). Therefore, section 501(f)(2)(B) of the FD&C Act requires that a PMA for such devices be filed within 90 days of the date of issuance of this final order. If a PMA is not filed for such devices within 90 days after the issuance of this final order, the devices will be deemed adulterated under section 501(f) of the FD&C Act.

Also, a preamendments device subject to the order process under section 515(b) of the FD&C Act is not required to have an approved investigational device exemption (IDE) (see part 812 (21 CFR part 812)) contemporaneous with its interstate distribution until the date identified by FDA in the final order requiring the filing of a PMA for the device. At that time, an IDE is required only if a PMA has not been filed. If the manufacturer, importer, or other sponsor of the device submits an IDE application and FDA approves it, the device may be distributed for investigational use. If a PMA is not filed by the later of the two dates, and the device is not distributed for investigational use under an IDE, the device is deemed to be adulterated within the meaning of section 501(f)(1)(A) of the FD&C Act, and subject to seizure and condemnation under section 304 of the FD&C Act (21 U.S.C. 334) if its distribution continues. Other enforcement actions include, but are not limited to, the following: Shipment of devices in interstate commerce will be subject to injunction under section 302 of the FD&C Act (21 U.S.C. 332), and the individuals responsible for such shipment will be subject to prosecution under section 303 of the FD&C Act (21 U.S.C. 333). FDA requests that manufacturers take action to prevent the further use of devices for which no PMA has been filed.

1. Transilluminator for Breast Evaluation

On January 11, 1991, the Obstetrics and Gynecology Devices Panel recommended that transilluminator devices for breast evaluation be classified into class III and subject to premarket approval to provide reasonable assurance of the safety and effectiveness of the device. The panel concluded that there were no published studies or clinical data demonstrating the safety and effectiveness of the device. The panel indicated that the device presents a potential unreasonable risk of illness or injury to the patient if the clinician relies on the device. The panel found further that although the device's illumination level, wavelength, and image quality can be controlled

through tests and specifications, insufficient evidence exists to determine that special controls can be established to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

In addition, the Radiologic Devices Panel considered the classification of the transilluminator for breast evaluation on April 12, 2012, and expressed concerns regarding the effectiveness of the device and the potential for delayed diagnosis. The panel determined that general controls and special controls are not sufficient to provide a reasonable assurance of safety and effectiveness of the device for the diagnosis of cancer, other conditions, diseases, or abnormalities. Accordingly, the panel concluded that the device should remain in class III. FDA agreed and continues to agree with the recommendations of both panels and is aware of no information submitted in response to the 515(i) Order (74 FR 16214, April 9, 2009) or otherwise available to FDA that would support a different classification. The Agency notes that the device has fallen into disuse and that the published data are not adequate to demonstrate the safety and effectiveness of the device.

FDA received and has considered two comments on this proposed order, as well as one comment received in response to the August 25, 2010 (75 FR 52294), proposed rule as discussed in section II of this document.

2. SHS Devices for the Treatment of Hepatic Coma and Metabolic Disturbances

FDA held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to SHS devices on July 27, 2013. The panel unanimously recommended that SHS devices for the treatment of hepatic coma and metabolic disturbances should remain in class III (subject to premarket approval application) because there was insufficient information to establish special controls, and that the application of general controls is insufficient to provide a

reasonable assurance of safety and effectiveness for SHS devices that are life-supporting and life-sustaining and, because there is no clear benefit from the use of these devices in these vulnerable populations, there is a potential unreasonable risk of illness or injury when used for the treatment of hepatic coma and metabolic disturbances. The panel also unanimously supported FDA's conclusion that the effectiveness of SHS when indicated for the treatment of hepatic coma and metabolic disturbances had not been established through adequate scientific evidence. FDA published a proposed order in the Federal Register of April 4, 2013. FDA received and has considered two comments on this proposed order, as well as one comment received in response to the February 17, 2012, proposed rule as discussed in section II of this document.

B. Reclassification

FDA is reclassifying SHS devices when indicated for the treatment of poisoning and drug overdose from class III to class II (special controls). Section 513(e) of the FD&C Act governs reclassification of classified preamendments devices. This section provides that FDA may, by administrative order, reclassify a device based upon "new information." FDA can initiate a reclassification under section 513(e) or an interested person may petition FDA to reclassify a preamendments device. The term "new information," as used in section 513(e) of the FD&C Act, includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland-Rantos Co. v. United States Department of Health, Education, and Welfare, 587 F.2d 1173, 1174 n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent action where the reevaluation is made in light of newly available authority (see Bell, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F.Supp. 382, 388-391 (D.D.C. 1991)), or in light of changes in “medical science” (Upjohn, 422 F.2d at 951). Whether data before the Agency are old or new data, the “new information” to support reclassification under section 513(e) must be “valid scientific evidence,” as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Association v. FDA, 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

FDA relies upon “valid scientific evidence” in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the “valid scientific evidence” upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)). Section 520(h)(4) of the FD&C Act, added by FDAMA, provides that FDA may use, for reclassification of a device, certain information in a PMA 6 years after the application has been approved. This includes information from clinical and preclinical tests or studies that demonstrate the safety or effectiveness of the device but does not include descriptions of methods of manufacture or product composition and other trade secrets.

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments to the public docket. FDA published a proposed order in the Federal Register on April

4, 2013. FDA held a meeting of a device classification panel described in section 513(b) of the FD&C Act with respect to SHS devices on June 27, 2013

(<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/ucm358362.htm>). The panel unanimously recommended that SHS devices for the treatment of poisoning and drug overdose, a preamendments class III device, should be reclassified into class II because the application of general controls and special controls are sufficient to provide reasonable assurance of safety and effectiveness for SHS devices when intended for these uses. The panel also generally agreed with FDA's conclusion that the available scientific evidence is adequate to support the safety and effectiveness of SHS devices indicated for treatment of poisoning and drug overdose, although one member was concerned with the age of the data on which FDA's conclusions are based. The panel further agreed that the special controls identified by FDA were appropriate to mitigate the relevant risks to health for this use, although there was a fairly strong consensus for adding specificity with regard to specific elements to be removed by this therapy and to collect further clinical data. The identified special controls require both testing and labeling regarding the drugs and/or poisons the device has been demonstrated to remove, and the extent for removal/depletion of the substances. The special controls also require that a summary of the clinical experience with the device, including a discussion and analysis of the device safety and performance and a list of adverse events observed during the testing, be provided. These special controls address the panel's recommendations.

FDA received and has considered two comments on this proposed order, as discussed in section II of this document, as well as one comment on the prior proposed rule (77 FR 9610).

II. Public Comments in Response to the Proposed Rule and Proposed Order

A. Transilluminator for Breast Evaluation

In response to the August 25, 2010, proposed rule (75 FR 52294 at 52299) and the April 4, 2013, proposed order to maintain the class III classification and require the filing of a PMA for the transilluminator for breast evaluation, FDA received three comments.

Two of the comments supported the call for PMAs for this device. The other comment suggested the transilluminator for breast evaluation be reclassified as a class I device. FDA disagrees. FDA convened a meeting of the Radiological Devices Panel on April 12, 2012, as discussed in section I of this document, which was announced in a notice in the Federal Register on February 28, 2012 (77 FR 12064), that considered the information provided in the comment and the suggested class I status for this device. After considering the information provided in the comment and other available information, the panel determined that the device presents a potential unreasonable risk of illness or injury and that general controls and special controls are not sufficient to provide a reasonable assurance of safety and effectiveness of the transilluminator for breast evaluation for the diagnosis of cancer, other conditions, diseases, or abnormalities and recommended the device remain in class III. FDA concurs with the panel's recommendation.

B. SHS Devices for the Treatment of Hepatic Coma and Metabolic Disturbances

In response to the February 17, 2012, proposed rule and the April 4, 2013, proposed order to maintain the class III classification and require the filing of a PMA for SHS devices for the treatment of hepatic coma and metabolic disturbances, and to reclassify sorbent hemoperfusion devices into class II (special controls) when indicated for the treatment of poisoning and drug overdose, FDA received three comments.

The first comment disagreed with FDA's intent to reclassify SHS devices for the

treatment of poisoning or drug overdose to class II, stating: “The Food and Drug Administration’s (FDA’s) proposal for these devices raises fundamental questions about whether the Center for Devices and Radiological Health is following the law regarding the regulation of devices that are life-sustaining or life-supporting.” The commenter suggested that the devices proposed to be reclassified “are high-risk devices that can cause serious injury and death, and therefore they should remain in class III and be reviewed through the premarket approval process for all indications.” FDA disagrees with this comment. According to section 513(a)(1)(C) of the FD&C Act, a class III device is defined as a device which (1) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (2) cannot be classified as a class II device because insufficient information exists to determine that the special controls...would provide reasonable assurance of its safety and effectiveness, and (3) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or (4) presents a potential unreasonable risk of illness or injury. Although FDA considers SHS devices for the treatment of poisoning and drug overdose to be life-supporting or life-sustaining, a viewpoint which was supported by the panel members at the June 27, 2013, device classification panel meeting (2013 Panel), FDA believes that based on the available evidence, special controls, in addition to general controls, will provide a reasonable assurance of safety and effectiveness.

FDA also believes that, while the risks to health posed by SHS devices may be similar for its various uses, their severity in terms of patient outcomes and mitigation strategies are different for the drug overdose and poisoning uses, compared to the hepatic coma and metabolic

disturbances uses. This viewpoint was supported by the 2013 Panel, as also described in section I.B. The panel provided the following rationale for recommending that SHS devices, when indicated for drug overdose and poisoning be reclassified to class II: (1) The special controls listed would be effective in providing a reasonable assurance of safety and effectiveness and (2) the risk/benefit data demonstrates that SHS devices for drug overdose and poisoning do not pose a potential unreasonable risk of illness or injury. Therefore, FDA disagrees that SHS devices intended for the treatment of poisoning and drug overdose should remain classified as class III devices.

The second commenter responded to the proposed order, reiterating the commenter's previous comments to the 2012 proposed rule. They stated their continued support for the requirement of PMAs for SHS devices because they pose substantial risks and the benefits of these devices are "unknown" and there is "limited scientific evidence" regarding their effectiveness. They also reiterated their strong opposition to the reclassification of SHS devices for the treatment of poisoning and drug overdose. They cited FDA's statement that "the device may lead to the failure to remove drugs in the treatment of poisoning or drug overdose" as one of the reasons for supporting their PMA recommendation and believe that it is inappropriate to reclassify SHS devices for any indication. FDA continues to disagree with this comment and believes that the available scientific evidence supports the effectiveness of SHS devices for the treatment of poisoning and drug overdose. For drug overdose and poisoning cases, there is typically knowledge of the substance(s) which caused the overdose or poisoning, and SHS devices can be labeled to identify the specific substances or types of substances with which they can be used. Since the offending substances can often be identified in cases of poisoning or drug overdose, the SHS devices chosen to treat these problems can be tested with the specific

substances to demonstrate their removal capabilities and the extent of removal that may be expected. As noted previously in response to Comment 1, the 2013 Panel agreed with the FDA's conclusion of reclassification for SHS devices when intended for drug overdose and poisoning and further agreed that the special controls were appropriate to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness for these patient populations.

The commenter also noted that SHS devices for the treatment of hepatic coma and metabolic disturbances have a long list of health risks including platelet loss, blood loss, hypotension, toxic reactions, metabolic disturbances, and electrical shock, while there is "no proof that the device provides clinical improvement in hepatic coma and metabolic disturbances." Further, they "strongly support FDA's class III PMA recommendation, so that these products could not be sold unless new data are provided that prove their safety and efficacy for this indication." FDA agrees that SHS devices intended for the treatment of hepatic coma or metabolic disturbances be kept as class III devices for which a PMA is required to be filed. Although FDA has identified the risks to health posed by these devices in hepatic coma and metabolic disturbances uses, we believe we cannot adequately identify mitigation strategies for these risks, as they apply to these patient populations. Given the limited study of these devices and lack of evidence of clinically meaningful effectiveness for their use in the treatment of hepatic coma or metabolic disturbances, FDA does not believe that there is sufficient evidence to determine that special controls would provide reasonable assurance of safety and effectiveness for these patient populations. The panel unanimously agreed that these devices, when used for hepatic coma and metabolic disturbances, should remain in class III. They also stated that it is appropriate to maintain SHS devices for hepatic coma and metabolic disturbances in class III because they are life-supporting and life-sustaining and, because there is no clear benefit from

the use of these devices in these vulnerable populations, there is a potential unreasonable risk of illness or injury.

The third commenter stated that “Premarket approvals are necessary to establish the safety and efficacy of [the SHS devices] and prove that [the] possible benefits outweigh these substantial known risks.” They “agree with the FDA’s conclusion that the safety and effectiveness of sorbent hemoperfusion devices has not been established by adequate scientific evidence for the treatment of hepatic coma, because only a few randomized, controlled trials have been conducted using this device, and these were small, poorly designed, and not adequately powered.” They also “agree with the FDA that ‘bench testing is not adequate in establishing the devices’ safety and effectiveness, particularly since characterizing a sorbent hemoperfusion system’s performance and adsorption capabilities has not correlated to patient outcomes, such as resolution of the patients’ hepatic coma, or improvements in mortality.’ Moreover, they note that ‘there is no consensus [within the scientific literature] on the clinical endpoints necessary to adequately evaluate sorbent hemoperfusion devices for the treatment of hepatic coma and metabolic disturbances or on the patient populations who will benefit the most from the use of these devices.’” FDA agrees with this comment regarding the intended use of hepatic come and metabolic disturbances.

With respect to the reclassification proposal concerning SHS devices for the treatment of poisoning and drug overdose, the commenter stated “The fact that quick removal of a poison or drug can generally be expected to impact clinical outcomes does not establish that sorbent hemoperfusion is effective in treating poisoning and drug overdose. Several alternative mechanisms are available to remove poisons and drugs from the body, including (1) allowing the human body to clear a drug from the bloodstream through endogenous means (i.e. in absence of

any enhanced assistance) and (2) hemodialysis. Hemodialysis is more effective at removing water-soluble low molecular weight compounds and is considered preferable to hemoperfusion because it will also correct a concurrent acid-base disturbance. It is also generally better understood and more widely available than hemoperfusion. Hemoperfusion treatment carries substantial risks, and death or long-term morbidity may result due to complications from treatment. In order to assess whether these substantial risks are outweighed by potential benefits, the device must be compared with alternative approaches in well-controlled clinical investigations.” FDA disagrees with this comment in part. While hemodialysis may be more widely used as a first line therapy for drug overdose and poisoning, especially for water-soluble low molecular weight compounds, not all drugs and poisons are water-soluble. Hemoperfusion has been demonstrated to effectively remove lipids and protein-soluble substances (e.g., barbiturates, digitalis, carbamazepine, methotrexate, acetaminophen, and paraquat), as well as some water-soluble substances. Sorbent hemoperfusion system devices can be sufficiently tested on the bench for their removal capabilities using drugs and substances typically associated with overdoses and poisonings, and labeled to indicate which drugs or poisons are preferentially removed by hemoperfusion and the extent of their removal. The number of treatments required for the majority of cases of drug overdose or poisonings would be expected to be low depending on the degree of overdose, patient symptomatology, and the timing of the treatment with relation to the introduction of the toxin, thus minimizing the risks to health posed by the device. There is ample literature to establish the safety of hemoperfusion for drug overdose and poisoning. The published literature was presented to and discussed with the 2013 Panel, which helped to identify the risks to health posed by the device, and FDA believes that these known risks can be mitigated with the special controls identified. The panel agreed with reclassifying SHS devices for the

intended use of drug overdose and poisoning, and stated that FDA's list of risks to health is comprehensive and that these risks should be adequately mitigated by the special controls identified.

The commenter also opposed reclassification of SHS devices for drug overdose into class II on the ground that the proposed special controls will not adequately deter off-label use of these devices for treatment of hepatic coma and metabolic disturbances, conditions that are far more prevalent in the general population than accidental poisonings or drug overdoses. They state that they "believe that there will be substantial financial incentives for potentially harmful off-label use of these devices, and the proposed protections will fail to adequately deter such use." FDA disagrees with this comment in that we regulate the use of a device as indicated by the party offering the device for interstate commerce. The intended uses for SHS devices are limited by the codified classification.

III. The Final Order

FDA is adopting its findings as published in the preamble of the proposed order (78 FR 20268) by issuing this final order to require the filing of a PMA for the transilluminator for breast evaluation and SHS devices for the treatment of hepatic coma and metabolic disturbances under section 515(b) of the FD&C Act.

In addition, FDA is issuing this final order under section 513(e) of the FD&C Act to reclassify SHS devices for the treatment of poisoning and drug overdose from class III to class II and establish special controls. This final order will revise 21 CFR part 876.

A. Transilluminator for Breast Evaluation and SHS Devices for the Treatment of Hepatic Coma and Metabolic Disturbances

Under the final order, a PMA is required to be filed on or before 90 days after the date of publication of the final order in the Federal Register, for any of these class III preamendments devices that were in commercial distribution before May 28, 1976, or that has been found by FDA to be substantially equivalent to such a device on or before 90 days after the date of publication of the final order in the Federal Register. An approved PMA is required to be in effect for any such devices on or before 180 days after FDA files the application. Any other class III preamendments device subject to this order that was not in commercial distribution before May 28, 1976, is required to have an approved PMA in effect before it may be marketed.

If a PMA for any of the class III preamendments devices is not filed on or before the 90th day past the effective date of this final order, that device will be deemed adulterated under section 501(f)(1)(A) of the FD&C Act, and commercial distribution of the device must cease immediately. The device may, however, be distributed for investigational use, if the requirements of the IDE regulations (part 812) are met.

B. SHS Devices Intended for the Treatment of Poisoning and Drug Overdose

Following the effective date of this final order, firms submitting a 510(k) premarket notification for a SHS devices intended for the treatment of poisoning and drug overdose will need either to (1) comply with the particular mitigation measures set forth in the special controls guideline or (2) use alternative mitigation measures, but demonstrate to the Agency's satisfaction that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the

safety and effectiveness of the devices. FDA has determined that premarket notification is necessary to provide reasonable assurance of safety and effectiveness of sorbent hemoperfusion devices for the treatment of poisoning and drug overdose, and therefore, this device type is not exempt from premarket notification requirements.

An applicant whose device was legally in commercial distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, who does not intend to market such device for the treatment of hepatic coma, and/or metabolic disturbances may remove such intended uses from the device's labeling by initiating a correction within 90 days after issuance of any final order based on this proposal. Under 21 CFR 806.10(a)(2) a device manufacturer or importer initiating a correction to remedy a violation of the FD&C Act which may present a risk to health is required to submit a written report of the correction to FDA.

IV. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) and 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Paperwork Reduction Act of 1995

This final order refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in part 812 have been approved under OMB control number 0910-0078; the collections of information in part 807, subpart E, have been approved under OMB

control number 0910-0120; the collections of information in 21 CFR part 814, subpart B, have been approved under OMB control number 0910-0231; and the collections of information under 21 CFR part 801 have been approved under OMB control number 0910-0485.

VI. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) provided for FDA to issue regulations to reclassify devices and section 515(b) of the FD&C Act provided for FDA to issue regulations to require approval of an application for premarket approval for preamendments devices or devices found to be substantially equivalent to preamendments devices. Sections 513(e) and 515(b) as amended require FDA to issue final orders rather than regulations, and FDASIA provides for FDA to revoke previously issued regulations by order. FDA will continue to codify reclassifications and requirements for approval of an application for premarket approval in the Code of Federal Regulations. Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended by FDASIA, in this final order, we are revoking the requirements in 21 CFR 876.5870 related to the classification of sorbent hemoperfusion system devices for the treatment of poisoning and drug overdose as class III devices and codifying the reclassification of these devices into class II.

List of Subjects

21 CFR Part 876

Medical devices.

21 CFR Part 892

Medical devices, Radiation protection, X-rays.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 876 and 892 are amended as follows:

PART 876--GASTROENTEROLOGY-UROLOGY DEVICES

1. The authority citation for 21 CFR part 876 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Revise § 876.5870 to read as follows:

§ 876.5870 Sorbent hemoperfusion system.

(a) Identification. A sorbent hemoperfusion system is a prescription device that consists of an extracorporeal blood system similar to that identified in the hemodialysis system and accessories (§876.5820) and a container filled with adsorbent material that removes a wide range of substances, both toxic and normal, from blood flowing through it. The adsorbent materials are usually activated-carbon or resins which may be coated or immobilized to prevent fine particles entering the patient's blood. The generic type of device may include lines and filters specifically designed to connect the device to the extracorporeal blood system. The device is used in the treatment of poisoning, drug overdose, hepatic coma, or metabolic disturbances.

(b) Classification. (1) Class II (special controls) when the device is intended for the treatment of poisoning and drug overdose. The special controls for this device are:

- (i) The device must be demonstrated to be biocompatible;
- (ii) Performance data must demonstrate the mechanical integrity of the device (e.g., tensile, flexural, and structural strength), including testing for the possibility of leaks, ruptures, release of particles, and/or disconnections under anticipated conditions of use;
- (iii) Performance data must demonstrate device sterility and shelf life;

(iv) Bench performance testing must demonstrate device functionality in terms of substances, toxins, and drugs removed by the device, and the extent that these are removed when the device is used according to its labeling, and to validate the device's safeguards;

(v) A summary of clinical experience with the device that discusses and analyzes device safety and performance, including a list of adverse events observed during the testing, must be provided;

(vi) Labeling must include the following:

(A) A detailed summary of the device-related and procedure-related complications pertinent to the use of the device;

(B) A summary of the performance data provided for the device, including a list of the drugs and/or poisons the device has been demonstrated to remove, and the extent for removal/depletion; and

(vii) For those devices that incorporate electrical components, appropriate analysis and testing must be conducted to verify electrical safety and electromagnetic compatibility of the device.

(2) Class III (premarket approval) when the device is intended for the treatment of hepatic coma and metabolic disturbances.

(c) Date premarket approval application (PMA) or notice of completion of product development protocol (PDP) is required. A PMA or notice of completion of a PDP is required to be filed with FDA by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], for any sorbent hemoperfusion system indicated for treatment of hepatic coma or metabolic disturbances that was in commercial distribution before May 28, 1976, or that has, by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE

FEDERAL REGISTER], been found to be substantially equivalent to any sorbent hemoperfusion device indicated for treatment of hepatic coma or metabolic disturbances that was in commercial distribution before May 28, 1976. Any other sorbent hemoperfusion system device indicated for treatment of hepatic coma or metabolic disturbances shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

PART 892--RADIOLOGY DEVICES

3. The authority citation for 21 CFR part 892 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

4. Revise § 892.1990(c) to read as follows:

§ 892.1990 Transilluminator for breast evaluation.

* * * * *

(c) Date premarket approval (PMA) or notice of completion of product development protocol (PDP) is required. A PMA or notice of completion of a PDP is required to be filed with FDA by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], for any transilluminator for breast evaluation that was in commercial distribution before May 28, 1976, or that has, by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER], been found to be substantially equivalent to any transilluminator for breast evaluation that was in commercial distribution before May 28, 1976. Any other transilluminator for breast evaluation shall have an approved PMA or declared completed PDP in effect before being placed in commercial distribution.

Dated: January 13, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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